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Four Sibs With Arterial Tortuosity: Description and Review of the Literature

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We described four offspring of a consanguineous couple with arterial tortuosity "syndrome" (ATS). The affected children had extensive arterial involvement although the clinical presentations were quite variable. Clinical manifestations included cutis laxa or soft/thin skin, joint laxity or contractures, and arachnodactyly. Aortic tortuosity and pulmonary artery aneurysms with or without peripheral stenoses were demonstrated in all four sibs. All three males had inguinal hernias. Inconsistent facial anomalies were downslanting palpebral tissues, beaked nose, micrognathia, and high-arched palate. Results of collagen type I and type III biosynthesis studies were normal on skin fibroblasts. Histologic findings on autopsy of one affected child showed arterial changes with disruption of elastic fibers of the media and fragmentation of the internal elastic membrane as well as mucosal and transmural necrosis of the stomach, small bowel, colon, and extensive necrosis of the liver. Coronary artery involvement was also seen in this child as well as biventricular hypertrophy. We conclude that ATS is an autosomal recessive connective tissue condition associated with diffuse arterial changes and involvement of the skin, joints, and other organs.

KEY WORDS: arterial tortuosity, connective tissue, internal elastic membrane, autosomal recessive

INTRODUCTION

Arterial tortuosity syndrome (ATS) is a rare disorder of uncertain inheritance pattern, characterized by arterial tortuosity, stenoses or aneurysms, and alteration of the vascular elastic fibers. A variable number of anomalies and connective tissue problems have been described over the past 3 decades in individual case reports [Ertugrul, 1967; Beuren et al., 1969; Lees et al., 1969; Wagstaff et al., 1970; Welch et al., 1971; Rasooly et al., 1988]. We describe the clinical and pathological characteristics of four sibs with this syndrome born to a consanguineous couple and suggest that ATS is an autosomal recessive connective tissue disorder with variable clinical presentation.

CLINICAL REPORTS

Sib 1

Patient III-3 (Fig. 1) was the 3160 g product of a term uncomplicated pregnancy and normal spontaneous vaginal delivery born to a 22-year-old gravida 3 para 2 Moslem mother of Yemeni descent. The mother and father are first cousins. Two older brothers (III-1 and III-2) were alive and well. The female infant was discharged with her mother at age 3 days. She was readmitted 2 weeks later for frequent vomiting and failure to thrive.

Gastrointestinal work-up was unremarkable. Radiological evaluation to rule out a bronchogenic cyst documented an enlarged ectatic vascular structure in the left middle mediastinum which most likely represented a dilated left carotid artery. MRI showed a vascular abnormality involving the aortic arch. Mild systemic hypertension was noted at this time. Cardiac catheterization demonstrated an elevated right systolic ventricular pressure of 50–60 mm Hg and main pulmonary artery pressure of 60/10 mm Hg. Cineangiography showed diffuse bilateral peripheral pulmonary artery stenoses with areas of post-stenotic dilatation. The aorta appeared elongated and the left subclavian and left carotid arteries were markedly tortuous. The left coronary artery had a tortuous "beaded" appearance.

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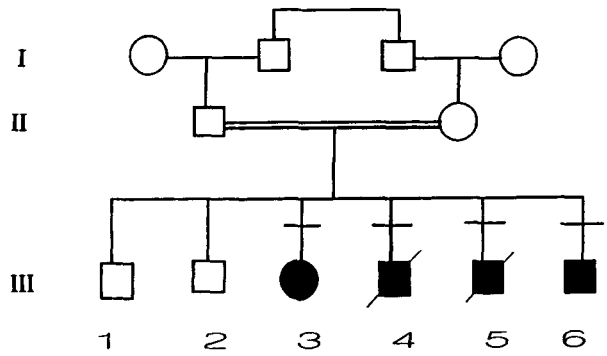

Fig. 1. Pedigree of family with ATS. ●, ■, affected individuals.

Fig. 2. Patient III-4. Feeding tube in place. Note brachycephaly, downslanting palpebrae and mild micrognathia. Overfolded helices and beaked nose not visible. Left cortical thumb and camptodactyly also evident.

The patient was well until age 3 years when she was readmitted with profuse diaphoresis, non-projectile vomiting, pallor, palpitations, and decreased stamina without headache or cyanosis. Physical examination showed slight frontal bossing, beaked nose, high arched palate, and pointed ears. Her skin was very soft and thin but was not hyperextensible. There were no scars or bruises. She exhibited increased mobility in the joints of the hands, hips, and ankles.

Skin fibroblasts grown in culture synthesized and secreted type I and type III procollagen normally. The procollagen chains showed normal electrophoretic mobility and conversion to collagen. Molecular analysis showed no evidence of a deletion of an elastin gene on chromosome 7.

Lymphocyte chromosomes were normal. Repeat angiography documented diffuse arteriopathy of unknown cause affecting systemic and pulmonary vessels. The abdominal aorta was small with tortuous branches; the pulmonary arteries showed multiple severe peripheral branch stenoses with suprasystemic right ventricular hypertension. At 7½ years of age this child had significant developmental delays; parents declined medical follow-up.

Sib 2

Patient III-4 (Fig. 1) was the 4,620 g product of a term uncomplicated pregnancy and normal spontaneous vaginal delivery born to a now 26-year-old gravida 4 para 3 mother. He was discharged home with his mother at age 2 days. At age 16 days he underwent bilateral herniorrhaphy as an outpatient, but required hospitalization over night because of dehydration. He was readmitted at age 2 months because of poor feeding, diaphoresis, tachypnea, and circumoral cyanosis. Chest film showed marked cardiomegaly with clear lung fields. Two-dimensional color Doppler echocardiography demonstrated a dilated right atrium and ventricle, biventricular hypertrophy, and a dilated main pulmonary artery. Moderate tricuspid and pulmonary valve insufficiency were noted. Physical examination demonstrated brachycephaly, downslanting palpebral tissues, overfolded helices, beaked nose, and mild micrognathia (Fig. 2), and arachnodactyly (Fig. 3) with persistent cortical thumbs and flexion contractures of the knees, left greater than right. Joint laxity was not apparent. Cutaneous findings included dramatic cutis laxa with decreased subcutaneous tissue and redundant nuchal skin without a prominent venous pattern. Herniorrhaphy scars were well healed.

Cardiac catheterization disclosed elevation of the right ventricular and main pulmonary artery pressures to near systemic levels (pulmonary artery pressure = 100/32, mean = 54 with right arm cuff arterial pressure 133/32). An interatrial communication with right to left shunting was noted. Pulmonary arteriograms demonstrated a grossly dilated, aneurysmal main pulmonary artery with abrupt narrowing of the right and left branch pulmonary arteries (Fig. 4). The pulmonic valve was relatively thick with evidence of pulmonary regurgitation. The aorta appeared tortuous and elongated (Fig. 5), resulting in compression of the

Fig. 3. Patient III-4. Hand demonstrating arachnodactyly and joint contractures.

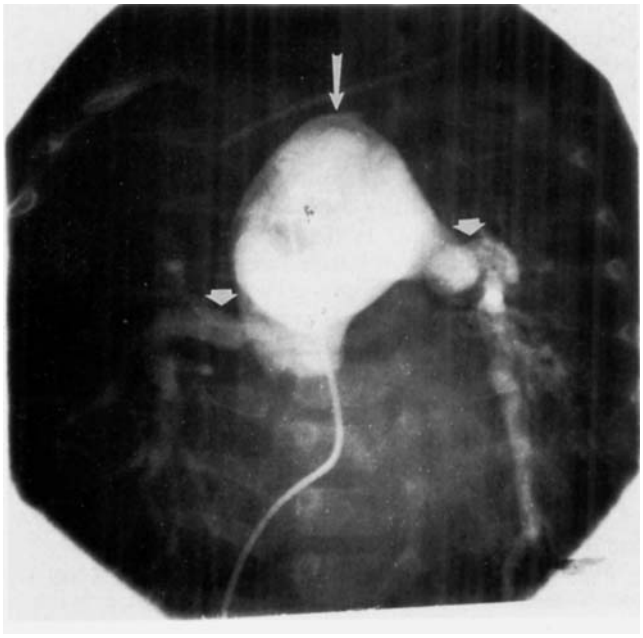

Fig. 4. Patient III-4. Pulmonary arteriogram. An aneurysmal main pulmonary artery (long arrow) and stenosis of the right and left pulmonary artery (short arrows) are noted.

left ventricle. The right ventricle was enlarged. The aortic branches to the head and neck were also quite redundant and tortuous. In addition, diffuse hypoplasia of the femoral veins, iliac veins and the infrahepatic portion of the inferior vena cava were noted.

The patient was discharged home on Digoxin, furosemide, and Captopril, but was readmitted shortly thereafter for respiratory distress and increasing cyanosis. Chest radiograph showed cardiomegaly with widening of the superior mediastinum. Nasogastric feeding was initiated to boost caloric intake and he was discharged 11 days later. At 3 months of age the patient died at home. Parents refused autopsy.

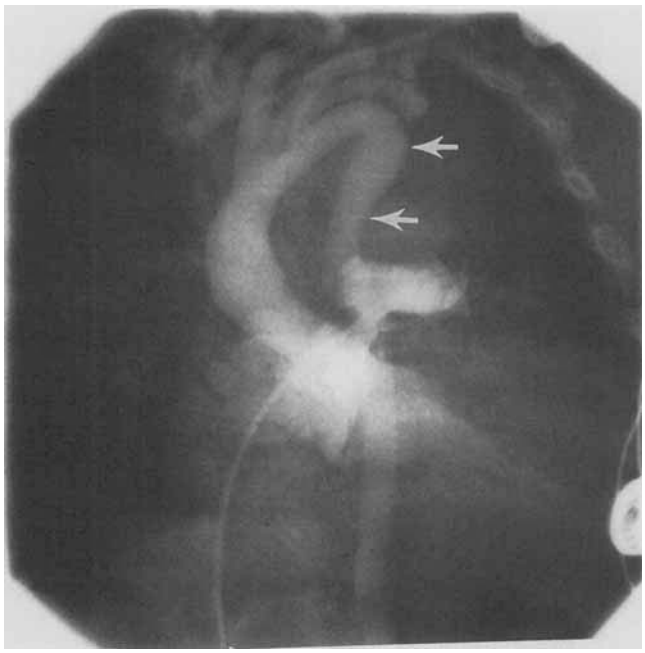

Fig. 5. Patient III-4. Left atrial angiogram. An elongated, tortuous aorta is seen (arrows).

Sib 3

Patient III-5 (Fig. 1) was the 3,720 g product of a term pregnancy complicated by prolonged rupture of membranes. He was born by normal spontaneous vaginal delivery to a now 27-year-old gravida 5 para 4 mother. He was discharged at age 3 days, when all cultures were negative. At birth he was noted to have a right inguinal hernia.

He fed well neonatally but presented at age 9 days with an incarcerated right inguinal hernia. He was referred to the emergency room and the hernia was easily reduced by the pediatric surgeon. However, at the time of this examination the infant was noted to have a fever of 38.4° C and was admitted to rule out sepsis. In addition he was considered irritable and cultures of blood, urine and cerebrospinal fluid were obtained. Within 24 hours abdominal distention, absent bowel sounds, and hypotension were noted. He was transferred to the pediatric intensive care unit.

An electrocardiogram demonstrated left ventricular hypertrophy. Echocardiography demonstrated normal intracardiac anatomy with inadequate visualization of the aortic arch. The infant became increasingly lethargic. His stool became guaiac positive, abdominal radiograph showed intestinal pneumatosis, and generalized seizures occurred. At laparotomy extensive intestinal necrosis was noted. The infant died at age 13 days.

Autopsy documented arterial tortuosity without minor anomalies, arachnodactyly or joint abnormalities. There was marked tortuosity of the coronary arteries (Fig. 6). Histologic examination of the arteries demonstrated fragmentation of the internal elastic membrane, disruption of elastic fibers of the media and a variable degree of intimal fibrosis (Fig. 7A,B). Some or all of these changes were noted in the aorta, pulmonary, coronary, mesocolic, renal, splenic and hepatic arteries, and portal vein. Histology showed no alterations in the elastic fibers within the lung parenchyma itself with changes restricted to branches of the pulmonary arteries. In addition, there were focal areas of full thickness necrosis of the stomach and extensive necrosis of the jejunum, ileum and cecum as well as focal ischemic changes of the colon. The liver had multifocal areas of coagulative necrosis, consistent with ischemic changes. Infarction of the spleen and kidneys, and biventricular cardiac hypertrophy were also present.

Sib 4

Patient III-6 (Fig. 1) was seen briefly at age 1 week following inguinal herniorrhapy. Birth history was not available. On exam he was noted to have downslanting palprebral tissues, pointed helices, micrognathia, and a pectus excavatum. Skin was noted to be quite soft with "doughy" subcutaneous tissue.

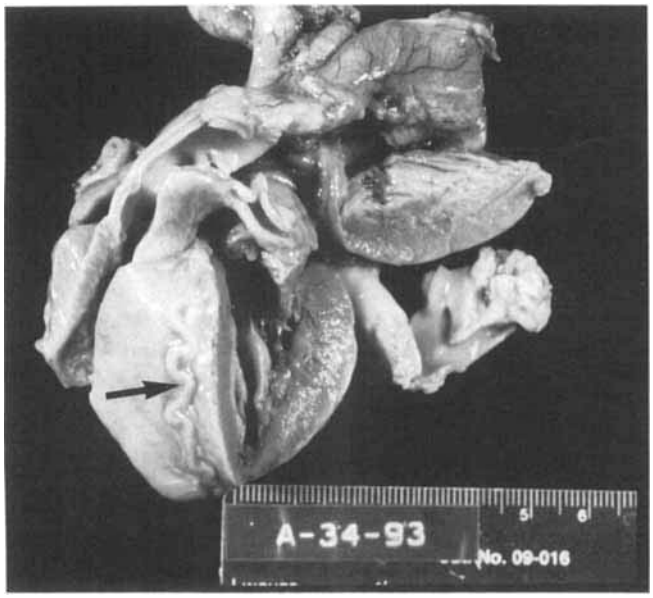

Fig. 6. Patient III-5. Gross appearance of the heart. Note the marked tortuosity of the left anterior descending artery, arrow.

Echocardiogram at this time demonstrated mild to moderate dilatation of the main pulmonary artery and right ventricle, elongated branches of the pulmonary arteries, and a tortuous aortic arch. An echocardiogram performed at age 6 weeks showed an atypical vascular plexus adjacent to the thymus. The patient was then lost to follow-up.

DISCUSSION

We describe four sibs from a consanguineous union affected with systemic arterial tortuosity and variable cutaneous, facial, and joint manifestations. Tables I, II, and III review the clinical and pathologic findings in our patients and those of previous reports.

Males appear to be affected more frequently with a male to female ratio of 7:4. The age of diagnosis varied from birth to 8 years, with a median age of 16 months. Of the 11 patients reviewed, 5 were dead, 4 alive, and 2 had no report of follow-up. Of the 5 who died, death occurred between birth and 4½ years with a mean age of 6 months.

Most reports imply that individuals with ATS have signs of a systemic connective tissue defect and therefore various disorders of connective tissue have been included in the clinical descriptions. Ehlers-Danlos was considered as the diagnosis in the 22-month-old boy reported by Lees et al. [1969] who clearly had the additional findings of widespread arterial involvement whereas Rasooly et al. [1988] postulated Larsen syndrome in his patient. Wagstaff et al. [1970] described a patient with congenital cutis laxa, recurrent pneumonias, and vascular abnormalities. Skin biopsy in this child showed decreased numbers of elastic fibrils with fibrillar fragmentation. The absence of typical signs of Ehlers-Danlos in first degree relatives of our patients and normal biosynthesis of types I and III collagen in our patient III-3 makes this clinical diagnosis less likely.

The most important clinical anomaly present in individuals with ATS is tortuosity of the aorta. Other clinical findings include aortic aneurysms and tortuosity and elongation of other major vessels. These changes were present to various degrees in all four patients. Pulmonary artery involvement was noted in most of the reported patients with aneurysmal dilatation of the main pulmonary artery and/or distal pulmonic stenoses which were also noted in three of our patients. Coronary artery tortuosity was observed in one patient [Ertugrul, 1967] and in III-5. Stenosis may also affect the aorta and peripheral systemic arteries as noted in our III-4 and by others [Beuren et al., 1969; Lees et al., 1969]. It is possible that imaging studies on a number of individuals were incomplete and additional vascular involvement was not found.

Microscopically, disruption of the arterial internal elastic membrane, intimal fibrosis, and medial changes were present in some of the patients reported [Ertugrul, 1967; Beuren et al., 1969; Lees et al., 1969; Welch et al., 1971]. Other individuals were noted to have increased elastic fibers in the media, possibly in response to chronic erosive forces [Beuren et al., 1969; Lees et al., 1969], while other patients, including III-5 had evidence of destruction and/or decrease of elastic fibers [Ertugrul, 1967; Welch et al., 1971]. The vascular changes appear to be responsible for pulmonary or systemic hypertension, congestive heart failure, coronary insufficiency or, as noted in III-5, mid-gut necrosis.

The minor anomalies, joint and skin involvement also appear to be quite variable in the reported individuals. The hyperelastic skin, joint laxity, and bird-like facial appearance, described by Lees et al. [1969], was similar to findings in our patients. Patient III-3 had minor anomalies and joint laxity but no skin hyperelasticity; III-4 had similar facial anomalies and hyperextensible skin but also had joint contractures (as opposed to joint laxity); III-6 had facial anomalies, soft skin, and firm subcutaneous tissues. In addition, marked arachnodactyly was present, also noted by Welch et al. [1971]. Patient III-5 had no cutaneous manifestations, normal joints, no arachnodactyly, and no minor anomalies. This might suggest that significant clinical variability may occur even within the same sibship. The inguinal hernias noted in our male patients were also reported by Welch et al. [1971]. The reason for this variable expression is unclear.

Joint and skin abnormalities may perhaps become more pronounced with age, whereas vascular alterations seem to appear early as demonstrated in our 1- and 2-week-old patients. Furthermore, subtle minor anomalies of the face, skin, and joints may have not been documented in earlier reports.

As more cases of ATS come to medical attention the full spectrum of clinical manifestations, prognosis and pathogenesis may be better delineated. With dramatic advances in our understanding of collagen, fibrillin, and connective tissue defects as well as improving

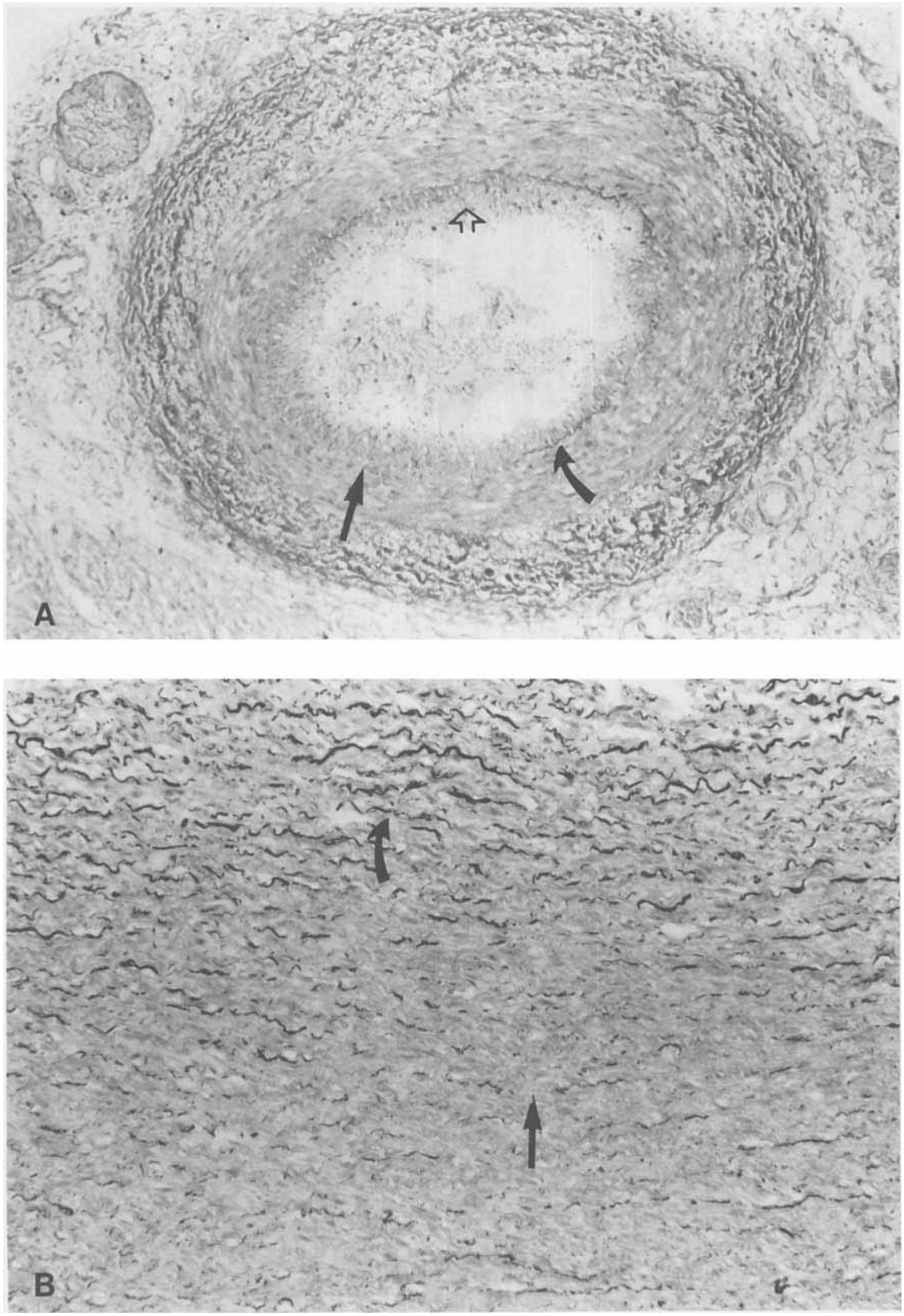

Fig. 7. A,B: Patient III-5. **A:** Coronary artery showing extensive disruption of the internal elastic membrane, straight arrow, and intimal hyperplasia, open arrow. Portion of the preserved internal elastic membrane indicated by curved arrow. Elastic Van-Gieson stain. **B:** Media of the aorta with marked disruption of elastic fibers, straight arrow. Better preserved elastic fibers in black, curved arrow. Elastic Van-Gieson stain.

TABLE I. General Characteristics and Non-Cardiovascular Findings in Arterial Tortuosity Syndrome

Case	Reference	Sex	Age at diagnosis	Survival	Consanguinity	Family history	Skin findings	Joint findings	Minor anomalies	Hernia	Arachnodactyly
1	Own	F	2 weeks	Alive 7½ years	+	+	Soft, thin	Hypermobile	Frontal bossing, pointed ears, beaked nose, high arched palate, micrognathia	−	−
2	Own	M	2 months	Died 3 months	+	+	Cutis laxa	Contractures	Brachcephaly, downslanted palpebrae, overfolded helices, beaked nose, micrognathia	+	+
3	Own	M	2 weeks	Died 2 weeks	+	+	−	−	−	+	−
4	Own	M	1 week	?	+	+	Soft, doughy	−	Downslanted palpebrae, pointed helices, micrognathia, pectus excavatum	+	−
5	Ertugrul	F	8 years	Alive 10 years	NS[a]	−	Telangiectasias	−	High arched palate	−	−
6	Beuren et al.	F	6 months	Died 18 months	NS	−	−	+	−	−	−
7	Lees et al.	F	3 months	Alive 4½ years	−	−	Hyperextensible bruisability	Hypermobile	Beaked nose, high arched palate, pectus excavatum, micrognathia	−	−
8	Wagstaff et al.	M	2 years	Alive 6½ years	NS	−	Cutis laxa	−	Lop ears, prognathism, long philtrum, malocculsion	+	−
8	Welch et al.	M	15 months	Died 2 years 4 months	+	+	Hyperextensible	Hypermobile	Epicanthal folds	+	−
9	Welch et al.	M	3 weeks	Died 6 months	+	+	Cutis laxa	Hypermobile	Upslanted palpebrae, soft floppy ears, epicanthal folds	−	+
10	Rasooly et al.	M	3 years	?	NS	−	−	Dislocations, cervical subluxations	Frontal bossing, high arched palate, cleft uvula, hypertelorism, downslanted palpebrae	−	−

[a]NS = not stated

TABLE II. ATS Clinical Signs and Symptoms

Case	Vomiting	Failure to thrive	Systemic HTN[a]	MPA HTN and/or peripheral stenoses[b]	Palpitations	Diaphoresis	Tachypnea	Dyspnea	Cyanosis	Other findings
1	+	+	+	+	+	+	–	–	–	–
2	–	+	–	+	–	+	+	–	+	–
3	+	–	–	–	–	–	–	–	–	Fever,small bowel obstruction, GI bleeding, pneumonia
4	–	–	–	?	–	–	–	–	–	–
5	–	–	–	?	+	–	–	+	–	Fever, abdominal pain, neck pulsations
6	–	–	–	+	–	+	–	–	–	–
7	–	–	–	+	–	+	–	–	–	–
8	–	–	+	?	–	–	+	+	–	Recurrent pneumonias, cor pulmonale, neck pulsations, seizures, gruff voice
9	–	–	–	–	–	–	–	–	–	Recurrent pneumonias
10	+	+	–	+	–	–	–	–	–	Pyloric stenosis, nephroptosis
11	–	–	–	?	–	–	–	–	–	Neck pulsations

[a] HTN, hypertension.
[b] MPA, main pulmonary artery.

TABLE III. ATS Cardiovascular Findings*

Case	Right ventricular hypertrophy	Left ventricular hypertrophy	Tortuosity site(s)	Aneurysm site(s)	Stenosis site(s)	Elastic fiber findings		Intimal fibrosis
						Fragm	Incr	
1	+	–	Carotid, subclavian, abdominal aorta branches, coronary	Pulmonary	Pulmonary	NE	NE	NE
2	+	–	Aorta, carotid	Pulmonary	Pulmonary, iliac veins, femoral arteries, inferior vena cava	NE	NE	NE
3	–	+	Coronary	–	–	+	–	+
4	–	–	Aorta, ? carotid	Pulmonary	–	NE	NE	NE
5	–	+	Aorta, carotid, femoral, brachial, iliac, renal, splenic, hepatic, celiac, superior and inferior mesenteric, intercostal	Aorta	–	+	–	–
6	+	–	Aorta, carotid, radial, renal, coronary	Pulmonary	Pulmonary	+	+	+
7	+	+	Aorta, coronary, intercostal	–	Aorta, pulmonary	–	+	+
8	NS	NS	Carotid, vertebral	Aorta	–	NE[a]	NE	NE
9	NS	NS	Aorta, femoral	Aorta, pulmonary	–	–	–	–
10	–	+	Aorta	Aorta	Aorta, pulmonary	NS	NS	NS
11	NS	NS	Carotid, cerebral, vertebral	Aorta, carotid, cerebral, superior mesenteric	–	NE	NE	NE

* Fragm, Fragmentation; Incr, Increased numbers; NE, Not examined; NS, Not stated.
[a] Skin histology showed elastic fibril fragmentation.

biotechnology, the underlying gene defect causing ATS may be identified in the near future.

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